

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

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|--|--|--|--|
| Applicant's or agent's file reference see form PCT/ISA/220 | | FOR FURTHER ACTION See paragraph 2 below | |
| International application No. PCT/GB2005/000806 | International filing date (day/month/year) 02.03.2005 | Priority date (day/month/year) 02.03.2004 | |
| International Patent Classification (IPC) or both national classification and IPC INV. A61K9/00 | | | |
| Applicant INSTITUTE OF OPHTHALMOLOGY | | | |

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | | |
|--|--|---|
| Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Date of completion of this opinion see form PCT/ISA/210 | Authorized Officer Schifferer, H Telephone No. +49 89 2399-7472 |
|--|--|---|



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 the international application in the language in which it was filed
 a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 on paper
 in electronic form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in electronic form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- the entire international application
- claims Nos. 22-25 in part

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- no international search report has been established for the whole application or for said claims Nos. 22-25 in part
- a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See Supplemental Box for further details

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|-------------------------------|------|--------|---------------|
| Novelty (N) | Yes: | Claims | 13,15,16 |
| | No: | Claims | 1-12,14,17-27 |
| Inventive step (IS) | Yes: | Claims | - |
| | No: | Claims | 13,15,16 |
| Industrial applicability (IA) | Yes: | Claims | 1-21, 26, 27 |
| | No: | Claims | |

2. Citations and explanations

see separate sheet

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IAP9 Rec'd PCT/PTO 28 AUG 2006

**WRITTEN OPINION OF THE
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- III Non establishment of opinion with regard to novelty, inventive step and industrial applicability
- 1) Claims 22-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
- V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability
- 1) Clarity
- 1.1) Claims 1 / (2-27 in part) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, namely by defining the agents incorporated by their action on the eye surface:
- a) an agent, that promotes any one or more of survival, health, cell attachment and normal differentiation of ocular surface, epithelial cells and optionally factors and agents that prevent squamous metaplasia,
b) agents that are capable of altering the fluid properties of a tear film,
c) agents capable of establishing and/or maintaining a stable tear film.
- This merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.
- 1.2) Inspite of 1.1 the search is considered appropriate and finalised, since the following concrete details were used:
for a) claim 6, page 7, line 36-page 9, line 29
for b) claim 7, page 11, lines 10-15
for c) page 11, lines 10-28.
- 1.3) Claims 1, 3 and corresponding passages in the present description use the term "licensed for pharmaceutical use". This is rendered merely unclear with regard to its exact scientific meaning and thus with regard to the scope of the invention (Article 6 PCT).
- 1.4) Claim 27 refers to a pharmaceutical preparation with reference to any one or more of the examples. Therefore, its content is left unclear according to Article 6 PCT, since its content is rather vague and unprecise.
- 2) Documents
The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

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- D1: US 5 200 393 A (WEINER ET AL) 6 April 1993 (1993-04-06)
- D2: US 6 565 861 B1 (TIFFANY JOHN MICHAEL ET AL) 20 May 2003 (2003-05-20)
- D3: EP 0 982 025 A (STOFFEL, WILHELM, PROF. DR) 1 March 2000 (2000-03-01)
- D4: DE 41 23 273 A1 (GRAMER, EUGEN, PROF. DR.MED. DR.JUR., 8700 WUERZBURG, DE;
GRAMER, EUGE) 14 January 1993 (1993-01-14)

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

- 3) Novelty - Article 33 (1) and (2) PCT
- 3.1) D1-D4 disclose ocular preparations comprising:
i) a carrier, ii) an agent that promotes survival, health, cell attachment, normal differentiation of ocular surface, epithelial cells, prevents squamous metaplasia, iii) an agent capable of altering the fluid properties of a tear film including at least one agent capable of establishing and/or maintaining a stable tear film.

This conclusion is based on the lists of concrete ingredients on pages 7-11 in present description.

D1:

carrier: water

agent promoting health of ocular surface: hyaluronic acid, insulin as hormone

agent for establishing/maintaining a stable tear film: monooleoyl phosphoethanolamine

preservative: no benzalkonium chloride

other inactive ingredients: buffer

D2:

carrier: water

agent promoting health of ocular surface: lipid binding protein (such as lysozyme, lactoferrin, IgA, [beta]-lactoglobulin, concentration of 0.01 to 50 mg/mL), electrolytes

agent for establishing/maintaining a stable tear film: phospholipids, glycolipids, sphingolipids

preservative: benzalkonium chloride

other inactive ingredients: buffer

200-500 mOsm/kg

active agent: mucolytic agent.

D3:

carrier: water

agent promoting health of ocular surface: lipophilic ionic compound (gangliosides, sulfatides, diacyllipids, dialkyllipids

agent for establishing/maintaining a stable tear film: glycerophospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol), cholesterol in a glycerophospholipid:cholesterol molar ratio up to 1:1, sphingolipids in a glycerophospholipid:sphingolipid molar ratio of 20:1 to 2,5:1

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preservative: may contain benzalkonium chloride
other inactive ingredients: buffer
active agents: antibiotics, antiviral drugs, cytostatic drugs, antimycotic drugs, wound healing substances, diagnostic markers for Cornea lesion

D4:

carrier: carbomer, water
agent promoting health of ocular surface: glucose
agent for establishing/maintaining a stable tear film: -
preservative: thiomersal, no benzalkonium chloride
other inactive ingredients: buffer

- 3.2) In the light of D1 -D4 (see sections V-2, 3.1) and under consideration of section III- 1., V-1.1-1.4, the subject-matter of claims 1-12,14,17-27 is considered not novel according to Article 33 (1) and (2) PCT.
- 3.3) Consequently, - under consideration of III- 1., V-1.1-1.4. - the subject-matter of claims 13, 15, 16 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D4.
- 4) Inventive Step - Article 33 (1) and (3) PCT
- 4.1) The problem posed in the present application was the treatment of ocular surface disorders.

The solution according to the Applicant was a pharmaceutical preparation suitable for the use in the eye comprising: i) a carrier, ii) ingredients promoting the survival, health, cell attachment, differentiation of ocular surface, iii) one or more agents capable of altering the fluid properties of a tear film including at least one agent capable of establishing and/or maintaining a stable tear film.

D2 which is regarded closest prior art discloses an ophthalmological pharmaceutical preparation comprising the following components:

- carrier: water
- agent promoting health of ocular surface: lipid binding protein (such as lysozyme, lactoferrin, IgA, [beta]-lactoglobulin, concentration of 0.01 to 50 mg/mL), electrolytes
- agent for establishing/maintaining a stable tear film: phospholipids, glycolipids, sphingolipids
- preservative: benzalkonium chloride, besides sodium perborate, EDTA
- other inactive ingredients: buffer
- 200-500 mOsm/kg
- active agent: mucolytic agent.

D2 does not disclose the surface tension, the viscosity and compositions of creams, ointments, gels.

It appears to be obvious to a person skilled in the art to derive the use of other ocular pharmaceutical forms as well as surface tension/viscosity for drops from formulations already obtained in galenics.

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Unexpected or surprising effects do not seem to be connected with these aforementioned points.

- 4.2) Therefore, under provision of III- 1., V-1.1-1.4, the subject-matter of claims 13, 15, 16 is obvious to a person skilled in the art due to general textbook knowledge. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

5) Industrial Applicability

For the assessment of the present claims 22-25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.